Summary Growth Factors

FDA Approved Indications and Dosages

Drug	Manufacturer	Indication(s)	Dosage	Availability
mecasermin [rDNA origin] injection (Increlex®)[1]	Tercica	Treatment for growth failure in children with severe primary IGF-1 deficiency or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.	Recommended dose: 0.04 to 0.08 mg per kg twice daily given subcutaneously. If tolerated well after one week the dose may be increased to 0.04 mg per kg per dose to a maximum of 0.12 mg per kg given twice daily.	Solution for injection: 40 mg/vial (10 mg per mL)
tesamorelin (Egrifta™)[2]	EMD Serono	Growth hormone releasing factor (GRF) analog indicated for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy	Recommended dose: 2 mg injected subcutaneously once daily	Lyophilized powder for injection: 1 mg tesamorelin/vial 10 mL sterile water for injection in separate vial

Overview

Growth hormone insensitivity or insulin-like growth factor-1 (IGF-1) deficiency is a variety of disorders characterized as the resistance to growth hormone. Growth hormone insensitivity can be defined by a deficiency in the production of growth hormone or peripheral action of IGF-1 on linear growth. Severe primary IGF-1 deficiency is due to a mutation of the growth hormone receptor or post-growth hormone receptor signaling. Severe primary IGF-1 deficiency is also characterized by the development of growth hormone inactivating antibodies in pediatrics with growth hormone gene deletion.[3] Patients are considered to have severe primary IGF-1 deficiency when the following criteria are met: height standard deviation score less than or equal to negative three, basal IGF-1 standard deviation score less than or equal to negative three, and normal or elevated growth hormone.[4,5]

HIV has become a chronic disease state resulting from the advancements in medications and the use of effective combination antiretroviral treatments. As a result, prescribers are now focusing attention to the adverse consequences of HIV antiretroviral medications. Soon after combination antiretroviral therapy was found effective in treating HIV infected patients adverse side effects from the medications were reported including metabolic changes, morphological abnormalities and lipodystrophy. Patients with HIV lipodystrophy were described as having a loss of subcutaneous fat in limbs, face, and buttocks and an accumulation of fat in other areas of the body including the abdominal viscera. Patients who have increased visceral abdominal

fat and waist circumference are at an increased risk for metabolic syndrome, cardiovascular disease, atherosclerosis, and diabetes mellitus.[6,7]

Special Usage Considerations[8,9]

Mecasermin (Increlex) contains human recombinant IGF-1 which is an essential hormonal mediator on linear growth. Growth hormone binds to receptors in the liver and other tissues to stimulate and secrete IGF-1 which then subsequently results in linear growth.

Tesamorelin (Egrifta) is an analog of human growth hormone-releasing factor and stimulates the human growth hormone-releasing factor receptors with potency similar to endogenous growth hormone-releasing factor. The growth hormone-releasing factor acts on the pituitary somatotroph cells to start the release of endogenous growth hormone. Growth hormone affects receptors on a variety of target cells including osteoblasts, chondrocytes, hepatocytes, myocytes, and adipocytes.

Mecasermin (Increlex) injectable solution maintains its stability when refrigerated. After opening Mecasermin (Increlex) it is stable for 30 days when stored in the refrigerator. Mecasermin (Increlex) should be administered by a subcutaneous injection to the upper arm, thigh, buttock, or abdomen. In order to avoid lipohypertrophy the injection sites should be rotated. Mecasermin (Increlex) should be given within 20 minutes of a meal or snack. If the patient is unable to eat before or after the injection then the injection should be withheld. The subsequent dose should not be adjusted in order to make up for missed doses.

Tesamorelin (Egrifta) should be stored in the refrigerator until use and the sterile water should be stored at room temperature. Tesamorelin (Egrifta) must be reconstituted with the sterile water provided and all unused reconstituted medication and used sterile water vials should be discarded. Do not refrigerate reconstituted tesamorelin (Egrifta). Tesamorelin (Egrifta) should be injected subcutaneously into the abdomen. The abdominal injection sites should be rotated to decrease adverse reactions and patients should not inject the medication into scar tissue, naval, or bruises.

Mecasermin (Increlex) and tesamorelin (Egrifta) and are contraindicated in patients with active malignancy. Prescribers should carefully evaluate tesamorelin (Egrifta) therapy in patients with a history of non-malignant neoplasms and patients with a history of treated and stable malignancies and consider the risks and benefits of its use. Tesamorelin (Egrifta) increases serum IGF-1 and prolonged elevations in IGF-1 on the development and progression of malignancies is unknown.

Patients with a hypersensitivity to mecasermin (Increlex) or any of its inactive ingredients should not use mecasermin (Increlex). Mecasermin (Increlex) is for subcutaneous injection only and should not be injected intravenously. If the patient has a closed epiphyses mecasermin (Increlex) should not be used.

Patients with a hypersensitivity to tesamorelin (Egrifta) or mannitol should not use tesamorelin (Egrifta). Tesamorelin (Egrifta) is contraindicated in patients with hypophysectomy, hypopituitarism, pituitary tumor/surgery, and head irradiation/trauma which have caused a disruption in the hypothalamic-pituitary axis. Tesamorelin (Egrifta) is contraindicated in pregnant patients.

Mecasermin (Increlex) and tesamorelin (Egrifta) can both affect glucose levels. Patients treated with tesamorelin (Egrifta) may experience glucose intolerance. Mecasermin (Increlex) has hypoglycemic affects and mecasermin (Increlex) dose titration may be needed until a well tolerated dose is established. Patients with variable food/caloric intake should be carefully monitored for adverse reactions. Tesamorelin (Egrifta) has been shown to raise HA_1C levels compared to placebo and also places patients at higher risk for developing diabetes mellitus. Patients taking mecasermin (Increlex) or tesamorelin (Egrifta) should have their glucose levels carefully monitored during therapy.

Long-term cardiovascular safety and benefit has not been established in tesamorelin (Egrifta). Therefore careful consideration of continuation of therapy is needed in patients who do not show a response in visceral adipose tissue reduction. Furthermore, tesamorelin (Egrifta) is not indicated for weight loss management and there is no data to support its use improves antiretroviral therapy compliance.

Mecasermin (Increlex) can cause intracranial hypertension. Discontinuation of therapy has shown sign and symptom resolution.

Patients treated with mecasermin (Increlex) have experienced slipped capital femoral epiphysis and any reports of knee or hip pain should be evaluated.

Patients with pre-existing scoliosis treated with Mecasermin (Increlex) have experienced progression of scoliosis. Patients should be monitored for progression of scoliosis.

Mecasermin (Increlex) contains benzyl alcohol which is associated with serious adverse events such as “gasping syndrome” and death especially in pediatric patients.

Tesamorelin (Egrifta) may cause fluid retention resulting in tissue tugor and musculoskeletal discomfort which is either transient or resolves after discontinuation of therapy.

Patients using tesamorelin (Egrifta) with acute critical illness due to open heart surgery, abdominal surgery, accidental trauma, and respiratory failure are at increased risk of mortality.

Adverse events in patients using mecasermin (Increlex) which occurred in five percent or higher of patients included: hypoglycemia, lipohypertrophy, bruising, otitis media, snoring, tonsillar hypertrophy, headache, dizziness, convulsions, vomiting, hypoacusis, fluid in middle ear, ear pain, abnormal tympanometry, cardiac murmur, arthralgia, pain in extremity, thymus hypertrophy, and ear tube insertion. The most common adverse reactions for tesamorelin (Egrifta) included hypersensitivity and injection site reactions including arthralgia (13.3 percent), pain in the extremity (6.1 percent), myalgia (5.5 percent), injection site erythema (8.5 percent), injection site pruritus (7.6 percent), and peripheral edema (6.1 percent).

Mecasermin (Increlex) is pregnancy category C. Tesamorelin (Egrifta) is pregnancy category X.

The safety and effectiveness of mecasermin (Increlex) has not been established in patients under two years old. The safety and effectiveness of tesamorelin (Egrifta) in pediatrics has not been established.

The safety and effectiveness of mecasermin (Increlex) and tesamorelin (Egrifta) has not been established in patients 65 years and older.

The safety and effectiveness of mecasermin (Increlex) or tesamorelin (Egrifta) has not been established in patients with hepatic or renal impairment.

Place in Therapy

Mecasermin (Increlex) is the only available product approved for the indication of long-term treatment of growth failure in pediatrics with severe primary IGF-1 deficiency or with growth hormone gene deletion with development of neutralizing antibodies to growth hormone. The patients who are not growth hormone deficient and will not respond well to exogenous growth hormone medications. Mecasermin (Increlex) should also not be used as a substitute for patients who require growth hormone therapy. Mecasermin (Increlex) should not be used on patients with secondary forms of IGF-1 deficiency and all thyroid and nutritional issues should be corrected prior to initiating mecasermin (Increlex) therapy. Mecasermin (Increlex) should not be used for weight loss management.[10]

Treatment of lipodystrophy can be difficult in HIV infected patients for several reasons. One method prescribers have used is to switch antiretroviral therapies to regimens which are less prone to increased visceral adipose tissue. However, success in reducing established visceral adipose tissue after switching antiretroviral therapies has been low indicating it may be a self-sustaining event and a potential restoration of health phenomenon. Antidiabetic medications have also been used to decrease visceral fat accumulation; however, the results are mixed and it is recommended that therapy be kept for patients with impaired glucose tolerance or diabetes mellitus and no evidence of lipoatrophy. Recombinant human growth hormone (rhGH) has been used with success in patients with AIDS-related wasting syndrome since it has been shown to improve muscle mass. However, studies have shown rhGH causes a reduction in visceral adiposity but supra-physiologic levels of IGF-1 and excess growth hormone symptoms occurred causing treatment cessation. Tesamorelin (Egrifta) offers a specific treatment option for the reduction of excessive abdominal fat in HIV patients with lipodystrophy as it appears to target the visceral fat compartment with little effect on subcutaneous fat or fat in the limbs.[11,12]

References

[1] Increlex [package insert]. Brisbane, CA; Tercica Inc; February 2011.
[2] Egrifta [package insert]. Rockland, MA; EMD Serono; November 2010.
[3] Fintini D, Brufani C, Cappa M. Profile of mecasermin for lonhg-term treatment of growth failure in children and adolescents with severe primary IGF-1 deficiency. Therapeutics and Clinical Risk Management. 2009; 5:553-559.
[4] Fintini D, Brufani C, Cappa M. Profile of mecasermin for lonhg-term treatment of growth failure in children and adolescents with severe primary IGF-1 deficiency. Therapeutics and Clinical Risk Management. 2009; 5:553-559.
[5] Micromedex. Available at: http://www.thomsonhc.com/home/dispatch. Accessed March 23, 2012.
[6] Moyle G, Moutschen M, Martínez E, et al. Epidemiology, Assessment, and Management of Excess Abdominal Fat in Persons with HIV Infection. ADIS Rev. 2010; 12(1): 3-14.
[7] The Medical Letter. Tesamorelin (Egrifta) for HIV-Associated Lipodystrophy. The Medical Letter. 2011; 53(1363): 34-35.
[8] Egrifta [package insert]. Rockland, MA; EMD Serono; November 2010.
[9] Increlex [package insert]. Brisbane, CA; Tercica Inc; February 2011
[10] Micromedex. Available at: http://www.thomsonhc.com/home/dispatch. Accessed March 23, 2012.
[11] Egrifta [package insert]. Rockland, MA; EMD Serono; November 2010.
[12] Moyle G, Moutschen M, Martínez E, et al. Epidemiology, Assessment, and Management of Excess Abdominal Fat in Persons with HIV Infection. ADIS Rev. 2010; 12(1):3-14.